REMARKS

Claims 41, 49, 53, 58, and 63 have been amended. Claims 41-47 and 49-64 are now pending in this application. Support for the amendments is found in the existing claims and the specification as discussed below. Accordingly, the amendments do not constitute the addition of new matter. Applicant respectfully requests the entry of the amendments and reconsideration of the application in view of the amendments and the following remarks.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 41-62 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the written description requirement because the claims contain subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) has possession of the claimed invention at the time that the application was filed.

The claims comprise the limitation of "cultivating the E. coli host cell under a culture condition that induces lytic growth of said cell without lysis". The Examiner asserts that this phrase implies that it is the culture condition that induces lytic growth of said cell without lysis when it appears that the lytic growth without lysis is caused by the combination of mutations in the late genes of the lambda phage and that the only culture condition shown to actually induce lytic growth is maintenance of a lambda cI857 ts mutant at higher temperature (>32° C) and that there is no basis provided by the instant specification or prior art for envisioning conditions other than temperature control for a cI857 ts mutant.

In response, Applicants have amended claims 41, 49, 53, and 58 to recite that a temperature of less than about 32° C delays lysis of the cells and permits the production of the soluble, biologically-active protein. Support for this amendment is found in the present specification at page 6, line 10. Applicants submit that the present claims meet the written description requirements of 35 U.S.C. § 112, first paragraph.

In view of Applicants' amendments, reconsideration and withdrawal of this ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 41-62 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that claims 41, 49, 53, and 58 are unclear on two grounds. That "lytic growth without lysis" is unclear and that "a culture condition that induces growth...without lysis" is inaccurate. The Examiner suggest that amendment of the claims to clearly indicate whether the phrase "lytic growth without lysis" means that the cells do not lyse, and to amend the claim to more clearly indicate that the change in culture conditions only induces lytic growth.

In response, Applicants have amended claims 41, 49, 53, and 58 to recite that a temperature of less than about 32° C delays lysis of the cells and permits the production of the soluble, biologically-active protein. Support for this amendment is found in the present specification at page 6, line 10. This clarifies that while lysis occurs, the lysis is delayed until a desired level of protein production is reached. The claims have also been amended to recite that the cells are cultured under a temperature of less than 32 °C so that lysis is delayed and the soluble, biologically-active protein is produced.

In view of Applicants' amendments and arguments, reconsideration and withdrawal of the above ground of rejection is respectfully requested.

Rejection under 35 U.S.C. § 103(a)

Claims 63-64 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Murray et al. in view of the 1997 Novagen catalog.

The Examiner asserts that Murray et al. teach construction and use of lambda phages comprising mutations in genes affecting phage mediated lysis of the host for the purpose of increasing the expression of a desired heterologous gene carried by the phage (polA).
The Examiner further asserts that it was known at the time of Murray et al. that phage exhibiting delayed lysis to express a gene product from the bacteriophage lambda genome resulted in many copies of the gene of interest and amplification of the gene product and that Murray, et al. suggest the use of "delayed lysis" phage to amplify the expression of the polA gene product provided that a method of tightly regulating the expression of polA is developed. The Examiner suggests that the Novagen Catalog describes such a method (pET). The Examiner concludes that it would have been obvious to extend the teaching of Murray et al. to include a copy of the polA gene on a multicopy plasmid such as the pET system.

In response, the presently claimed invention differs significantly from the disclosure of Murray et al. in that Murray et al. does not teach the expression and high protein production of a eukaryotic protein from a plasmid with which the *E. coli* cell has been transformed. The polA

gene expressed by Murray et al is native to the *E. coli* host cell, even though it is expressed from the lambda genome. Consequently, it was not unexpected that the *E. coli* cell could efficiently produce a functional native protein from the transcript produced by lambda.

On the other hand, Applicants are producing eukaryotic, human proteins at high concentrations which can be used efficaciously to treat human disease conditions. Claim 63 has been amended to specifically recite that the expressed gene is of eukaryotic origin. Support for this amendment is found in Examples 4 and 5 of the present specification, which teach production of eukaryotic proteins in Applicants' claimed *E. coli* strains. Furthermore, the present specification at page 16, lines 7-14, teaches that recombinant interferon produced by the claimed method was successfully used to treat a variety of disease conditions in human patients. This could not have been predicted from the disclosure of Murray et al. Murray et al. merely teach the production of an endogenous *E. coli* protein, amplified by the use of bacteriophage lambda. Considerations such as proper translation and processing to produce a functional protein are not an issue for Murray et al. since the protein produced is endogenous to the host cell. On the other hand, it could not have been predicted from the teaching of Murray, et al. at the time of the claimed invention, that eukaryotic proteins could be produced at the levels achieved by Applicants by using bacteriophage lambda and delayed lysis. Thus, production of interferon that could be used effectively to treat human patients was totally unexpected.

Furthermore, in Applicants' Claim 63, the protein product is produced from a plasmid, not from the lambda genome. In contrast, Murray, et al. teach expression from the lambda phage.

While the Examiner further asserts that Murray et al. suggest the use of "delayed lysis" phage to amplify the expression the polyA gene product provided that a method of tightly regulating the expression of polA is developed, Murray et al. provide no suggestion beyond expression of polA and the suggestion of Murray et al. certainly cannot be extended to genes in general, particularly to eukaryotic genes.

Consequently, Murray et al. provide no teaching, suggestion or motivation for one of ordinary skill in the art to produce a biologically-active eukaryotic protein by growing a first strain of *E. coli* cells harboring a lambda bacteriophage with a temperature-sensitive mutation, lysing the *E. coli* cells to release the bacteriophage, lytically infecting a second strain of *E. coli* which has been transformed with a plasmid having at least one copy of an expressible gene encoding a biologically-active eukaryotic protein and culturing the second strain of *E. coli* cells

to produce a protein which is released to the media as a soluble, biologically active eukaryotic protein. The teaching of Murray et al. on prokaryotic proteins cannot be extended to eukaryotic proteins with any predictability of success. The Novogen Catalog merely describes an *E. coli* expression system and does not correct the defects of the primary reference discussed above.

In view of Applicants amendments and arguments, it is respectfully requested that this ground of rejection be withdrawn.

CONCLUSION

In view of Applicants' amendments to the claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: July 28, 2003

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